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FERTILITY AND STERILITY, vol. 38, no. 4, October 1982, pages 491-492, The American Fertility Society, US; R. PUNNONEN et al.: "Polyethylene glycol 4000 in the prevention of peritoneal adhesions"

*** Pages 491 492***

(73) Proprietor: **MEDIVENTURES INC.**
15415 East Jefferson Avenue
Grosse Pointe Park Michigan 48230(US)

(72) Inventor: **Henry, Raymond L.**
1841 Aline
Grosse Pointe Woods Michigan 48236(US)
Inventor: **Leach, Richard E.**
2624 17th Ave., N.W.
Rochester Minnesota 55901(US)

(74) Representative: **Gore, Peter Manson et al**
W.P. THOMPSON & CO.
Coopers Building
Church Street
Liverpool L1 3AB (GB)

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Description

The present invention relates generally to compositions for use in reducing postsurgical adhesions in the abdominal or thoracic cavity of mammals.

There is a need for a method and composition suitable for use in preventing adhesion formation/reformation in mammals following surgical injury to the peritoneal or pleural cavity, or organs situated therein.

According to Ellis in a review entitled "The Cause And Prevention of Post-operative Intraperitoneal Adhesions" in Surgery, Gynecology and Obstetrics for September 1971, volume 133, pages 497-509, at pages 502-503, the prevention of adhesions has been the subject of an enormous amount of work since the beginning of the twentieth century. According to Ellis, these attempts have included means of preventing the fibrin-coated walls of the intestine from reaching each other by distending the abdomen with oxygen or filling the abdomen with saline solution, paraffin, olive oil lanolin, concentrated dextrose solution, macromolecular solutions of all sorts, and silicones.

Caspi, Halperin, and Bukovsky in an article entitled "The Importance of Periadnexal Adhesions in Reconstructive Surgery for Infertility" appearing in Fertility and Sterility for March 1982, volume 31, number 3, pages 296-300, at page 299 indicate that despite experimental and clinical efforts in the prevention of adhesion formation following surgery, no major advances have thus far been achieved. The authors discuss the use of post-operative intraperitoneal installation of a mixture of hydrocortisone acetate, promethazine, and ampicillin. As an alternative method of treatment, a low molecular weight dextran (a glucocorticoid) was also instilled intraperitoneally in another group of patients. The authors conclude that the intraperitoneal installation of high doses of glucocorticoids combined with early hydrotubations seems to be a worthwhile method.

Musich and Behrman in an article entitled "Infertility Laparoscopy In Perspective: Review of 500 Cases" appearing in The American Journal of Obstetrics and Gynecology for June 1, 1982, pages 293-303, at page 300 in the discussion section of the article, disclose that there is a need to prevent adhesions subsequent to surgery in view of a study of 35 patients which indicated that 30 of these patients having previous tuboplasties had severe adhesions, one-third of which were judged to be inoperable.

High molecular weight dextran either alone or in combination with dextrose has been used in the prevention of peritoneal adhesions subsequent to surgery. Dextran is clinically standardized to a low molecular weight of about 75,000 by partial hydrolysis and fractional precipitation of the high molecular weight particles which normally have molecular weights of up to 200,000. Dextran is a polymer of glucose which has a chain-like structure and is produced from sucrose by Leuconostoc bacterial. In articles appearing in Fertility and Sterility, volume 33, number 6, June 1980, pages 660-662, Holtz, Baker, and Tsai and volume 34, number 4, October 1980, pages 394-395, by Holtz and Baker, results are reported of the adhesion reducing effects of a 32% (aqueous) solution of dextran 70 containing 10% dextrose (sold under the Trade Mark HYSKON by Pharmacia, of Piscataway, New Jersey, U.S.A. Holtz et al postulate several mechanisms of action in the prevention of peritoneal adhesions utilizing HYSKON including a simple mechanical separation of adjacent surfaces, termed a hydroflotation effect.

Project coordinator diZerega and several contributors have reported the results of a large study in an article entitled "Reduction of Post-operative Pelvic Adhesions with Intraperitoneal 32% Dextran 70: A Prospective, Randomized Clinical Trial" in Fertility and Sterility, volume 40, number 5, for November 1983, pages 612-619. The authors, at page 618, indicate that the use Dextran intraperitoneally has limitations such as, for example, the reported tendency of HYSKON to support bacterial proliferation and concern over the anaphylactoid potential of dextran. In addition, the benefit of Dextran 70 in preventing post-operative adhesions was shown to be limited to the more dependent regions of the pelvis.

Borten and Taymor in Obstetrics and Gynecology, volume 61, number 6, June 1983, pages 755-757 report in an article entitled "Recurrent Anaphylactic Reaction to Intraperitoneal Dextran 75 Used for Prevention of Postsurgical Adhesions". These authors indicate that anaphylactic reaction to Dextran administered intravenously is well documented and report such a reaction after intraperitoneal administration of Dextran.

Linsky in The Journal of Reproductive Medicine for January 1987, pages 17-20 in an article entitled "Adhesion Reduction in the Rabbit Uterine Horn Model Using an Absorbable Barrier, TC-7". These authors report that the use of a resorbable fabric barrier provides a significant reduction in post-operative adhesion formation and that no gross remnants of the fabric barrier material were noted, subsequent to initial placement, after a two week period.

Oelsner et al in The Journal of Reproductive Medicine for November 1987, volume 32, number 11, pages 812-814, report results of a comparison of sodium carboxylmethyl cellulose, 32% dextran 70, and

condroitin sulfate to prevent the formation of postoperative adhesions in the rabbit uterus. The authors report superior results with condroitin sulfate which is described as a member of a family of biochemical compounds referred to as glycosssaminoglycans (formerly termed mucopolysaccharides), to which hyaluronic acid, heparine sulfate and heparin also belong.

The use of ethylene oxide/propylene oxide block copolymers as surfactants for use in surgical scrub solutions and the topical application of 10% solutions of these copolymers to wounds is described in Edlich et al in the Journal of Surgical Research, volume 14, number 4, April 1973, pages 277-284. The test results indicate that the copolymers having an ethylene oxide: propylene oxide ratio of 4:1 provide less inflammatory response in a wound to which the copolymer is applied in comparison with a copolymer having an ethylene oxide: propylene oxide ratio of 1:4. There is no indication in Edlich et al or any prior art that such copolymers are useful in reducing post-operative adhesions.

European Patent Application No. 83108953.7 discloses a composition comprising polyethylene or polypropylene glycol which is said to be suitable for parenteral administration e.g. by injection.

The composition is disclosed as being useful to prevent unwanted tissue growth after operations or after inflammation.

It has now been found possible, to provide compositions for use in reducing post-surgical adhesion formation/reformation in mammals following surgical injury to the organs of the peritoneal or pleural cavity.

According to the present invention there is provided a composition for use in the treatment of the mammalian body by reducing post-surgical adhesion formation/reformation following surgical injury to mammalian peritoneal or pleural caivty tissue or organs situated therein which comprises a composite which is liquid at 4 °C and which is a gel at mammalian body temperature, said component comprising a polyoxyalkylene block copolymer of formula:

$$Y[(A)_n - E - H]_x \quad (I)$$

wherein A is an oxyalkylene moiety having an oxygen-carbon atom ratio of less than 0.5, x is at least 1 Y is derived from water or an organic compound containing x reactive hydrogen atoms, E is a polyoxyethylene moiety, n has a value such that the average molecular weight of A is at least 500, as determined by the hydroxyl number of an intermediate of formula

$$Y[(A)_n - H]_x \quad (II)$$

and the total average molecular weight of the polyoxyalkylene block copolymer is at least 5000.

Subsequent to deposition of the compositions of the invention in the peritoneal or pleural cavity of a mammal, the polyoxyalkylene block copolymer is absorbed by the tissues with which it is in contact and the block copolymer is eventually excreted in a non-metabolized form, mainly in the urine.

In addition to functioning as a means of reducing post-operative adhesion formation/reformation in mammals folowing surgical injury to the peritoneal or pleural cavity or organs situated therein, the polyoxyalkylene block copolymer is believed to provide an environment surrounding the surgical injury which accelerates the regrowth rate of the injured tissue. For instance, the polyoxyalkylene block copolymer can be instilled within the uterine cavity as a distending medium during diagnostic or operative intrauterine endoscopic procedures. This application has two advantages. First, since certain aqueous concentrations of the polymers form a clear gel, their use is well suited for visualization of the uterine cavity. Second, since these aqueous solutions form a clear gel at body temperature, the use of said solutions to separate the uterine cavity walls will diminish or prevent post-surgical adhesion formation.

Optionally, the polyoxyalkylene block copolymer can be utilized advantageously in combination with bacteriostatic or bactericidal agents and fibrinolytic agents.

The present invention provides compositions for use in reducing post-operative adhesion formation/reformation in mammals following surgical injury to the peritoneal or pleural cavity or organs situated therein. In this specification and claims, the terms "peritoneal" and "abdominal" cavity are used as synonyms, as are the terms "pleural" and "thoracic" cavity. The compositions can include at least one of a bacteriostatic or bactericidal agent, and a fibrinolytic agent.

The preferred aqueous compositions are prepared at concentrations so as to take advantage of the gelation properties of certain of the block copolymers. When certain polyoxyalkylene block copolymers are present in aqueous solutions at certain concentrations, preferably of 15% to 30% by weight, such compositions can provide liquid compositions at ambient temperatures or below which revert to gel compositions upon contact with living mammalian tissue.

Alternatively, useful compositions of the invention can include non-aqueous compositions comprising at least one polyoxyalkylene block copolymer in combination with a physiologically acceptable non-aqueous carrier liquid. It is believed that the non-aqueous compositions of the invention function to prevent the formation/reformation of adhesions subsequent to surgical injury by a mechanism of action which has been termed in the prior art "hydroflotation".

Thus the injured tissues are prevented from contacting adjacent tissues by the means of the inclusion of a foreign fluid in the peritoneal or pleural cavity. With respect to those aqueous compositions of the invention which are chosen from polyoxyalkylene block copolymers of the invention which when prepared at suitable concentrations form gels upon contact with living mammalian tissue, it is believed that the mechanism of action to prevent the formation/reformation of adhesions is, in addition to hydroflotation, properly characterized as the result of separating the adjacent mammalian tissues by a firm, adherent gel coating.

The polyoxyalkylene block copolymer compositions of the invention include at least one block copolymer as below defined, optionally in combination with at least one of an adjuvant such as, for example, a humectant, a bactericide, a bacteriostatic agent, and a fibrinolytic agent. The agent to prevent leucocyte migration also functions as an adjuvant. Desirably, the copolymer is applied to injured tissue in a major amount in combination with a minor amount of the adjuvant. Useful humectants include, but are not limited to glycerin, propylene glycol, and sorbitol. Useful bactericides which can be administered in admixture with the aqueous or non-aqueous compositions of the invention include antibacterial substances such as, for example β-lactam antibiotics, such as, for example cefoxitin, n-formamidoyl thienamycin and other thienamycin derivatives, tetracyclines, chloramphenicol, neomycin, gramicidin, bacitracin, sulfonamides; aminoglycoside antibiotics such as, for example, gentamycin, kanamycin, amikacin, sisomicin and tobramycin; nalidixic acids and analogs such as, for example, norfloxacin and the antimicrobial combination of fludalanine/pentizidone; nitrofurazones, and the like. Antihistaminics and decongestants such as, for example, pyrilamine, cholpheniramine, tetrahydrazoline, antazoline, and the like, can also be used in admixtures as well as anti-inflammatories such as, for example, cortisone, hydrocortisone, beta-methasone, dexamethasone, fluocortolone, prednisolone, triamcinolone, indomethacin, sulindac, its salts and its corresponding sulfide, and the like.

Useful leucocyte migration preventing agents, which can be used in admixtures include silver sulfadiazine, acetylsalicyclic acid, indomethacin, and Nafazatrom. Useful fibrinolytic agents include urokinase, streptokinase, tissue plasminogen activator (TPA), and acylated plasmin.

The block copolymer compositions of the invention usually comprise:

at least one polyoxyalkylene block copolymer of the formula (I)

$$Y[(A)_n - E - H]_x \quad (I)$$

wherein A is a polyoxyalkylene moiety having an oxygen/carbon atom ratio of less than 0.5, x is at least 1, but can be at least 2, Y is derived from water or an organic compound containing x reactive hydrogen atoms, E is a polyoxyalkylene moiety constituting at least 60% by weight of the copolymer, n has a value such that the average molecular weight of A is at least 500 and can be 900, as determined by the hydroxyl number of a hydrophobe base intermediate,

$$Y[(A)_n - H]_x \quad (II)$$

and the total average molecular weight of the copolymer is at least 5000.

Post-operative pelvic adhesions have been associated with infertility. Significant periadnexal adhesions have been found, as reported by Musich and Behrman, as previously cited, upon laparoscopy in 72% of 106 patients having unexplained infertility who had previously undergone various pelvic surgical procedures. Prevention of such adhesions has been proposed in the prior art by treatment with aqueous dextran solutions of low molecluar weight. The prior art use of aqueous dextran solutions (i.e., dextran 70 at 32% solids) has shown adverse reactions and little or no reduction of post-operative pelvic adhesions.

In addition, an oxidized cellulose fabric barrier (sold under the trade designation TC-7 by Johnson and Johnson Products, Inc., New Brunswick, New Jersey), which is resorbable subsequent to utilization, has been used in the prior art as a treatment to prevent adhesions to the peritoneum by preventing abutting injured organ surfaces from making contact therewith. Chondroitin sulphate solutions have also been proposed for intraperitoneal use in the prevention of adhesions in rabbits. Each of these proposed methods of avoiding post operative adhesions have disadvantages which are overcome by the method of the present invention.

The mechanism of action of all of these treatments is proposed to be the result of the persistent separation of adjacent surgically injured surfaces thus permitting healing to occur without the formation of fibrinous bands between abutting surfaces which are characterized as adhesions. For instance, upon injury to the peritoneum there results an outpouring of a serosanguinous exudate which is of a proteinaceous nature. This fluid subsequently coagulates, producing fibrinous bands between abutting surfaces that become subsequently organized by fibroblast proliferation to produce collagenous adhesions. This process is thought to be initiated and well advanced within the first three days subsequent to surgical injury.

The polyoxyalkylene block copolymers which are utilized in the compositions of the invention can be viscous liquids, pastes, or granular solids. Where the copolymers are pastes, they can be used alone or in admixture with an optional humectant or low molecular weight polyoxyalkylene block copolymer having a molecular weight of less than 5000. Mixtures of granular block copolymers with at least one of the low molecular weight block copolymers or the viscous liquid block copolymers are also useful. A physiologically acceptable non-aqueous carrier or water can also be optionally added. Preferably, the copolymers, which are viscous liquids, are used in combination with water as a carrier or a non-aqueous carrier.

When the compositions of the present invention are used in combination with water or an organic compound containing X reactive hydrogen atoms as a carrier, preferably the aqueous solutions have a block copolymer concentration which provides a free flowing liquid at ambient temperatures which gels upon contact with living mammalian tissue. Generally, the copolymers which are useful are selected from those defined above in formula I. Generally, the copolymer is selected from those copolymers which contain at least 60% by weight, preferably at least 70% by weight, and most preferably at least 80% by weight of the residue of ethylene oxide (polyoxyethylene moiety). Generally, the copolymers have a total average molecular weight of at least 5000, and form a gel at mammalian body temperature, when in an aqueous solution generally at a concentration of 10 to 40%, preferably 15 to 30% by weight and most preferably 18% to 25% by weight.

The proportion of carrier used is 60% to 90% by weight, preferably 70% to 85% by weight, and most preferably 75% to 82% by weight, based upon the total weight of the composition of the present invention. Useful polyoxyalkylene block copolymers which will form gels in such aqueous solutions can be prepared using a hydrophobe base (such as A in Formulae I and II) derived from propylene oxide, butylene oxide, or mixtures thereof. These block copolymers and representative methods of preparation are further generally described in US-A- 2 677 700, US-A-2 671 619; and US-A- 2 979 528.

Generally the polyoxybutylene-based block copolymers useful in the compositions of the invention are prepared by first condensing 1,2 butylene oxide with a water soluble organic compound initiator containing 1 to about 6 carbon atoms such as 1,4 butylene glycol or propylene glycol and at least 2 reactive hydrogen atoms to prepare a polyoxyalkylene polymer hydrophobe of at least 500, preferably at least 1000, most preferably at least 1500 average molecular weight. Subsequently, the hydrophobe is capped with an ethylene oxide residue. Specific methods for preparing these compounds are described in US-A- 2 828 345 and GB-A- 722 746.

Useful polyoxybutylene based block copolymers conform to the following generic formula:

$$HO(C_2H_4O)_b(C_4H_8O)_a(C_2H_4O)_bH \quad (III)$$

wherein a is an integer such that the hydrophobe base represented by (C_4H_8O) has a molecular weight of at least 500, preferably at least 1000 and most preferably at least 3000, as determined by hydroxyl number, the polyoxyethylene chain constituting at least 60%, preferably at least 70% by weight of the copolymer, and the copolymer having a total average molecular weight of at least 5000, preferably at least 10,000, and most preferably at least 15,000.

The copolymer is characterized in that all the hydrophobic oxybutylene groups are present in chains bonded to an organic radical at the former site of a reactive hydrogen atom thereby constituting a polyoxybutylene base copolymer. The hydrophilic oxyethylene groups are used to cap the polyoxybutylene base polymer.

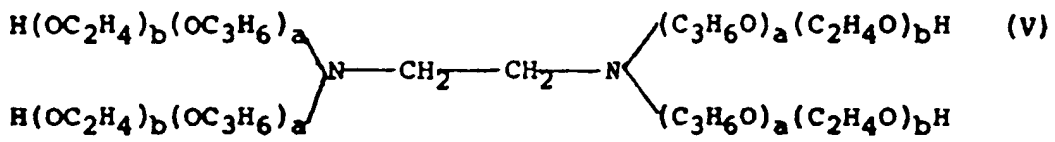
Polyoxyethylene-polyoxypropylene block copolymers which can be used to form aqueous gels can be represented by the following formula:

$$HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH \quad (IV)$$

wherein a is an integer such that the hydrophobe base represented by (C_3H_6O) has a molecular weight of at least 900, preferably at least 2500, most preferably at least 4000 average molecular weight, as determined by hydroxyl number; the polyoxyethylene chain constituting at least 60%, preferably at least

70% by weight of the copolymer, and the copolymer having a total average molecular weight of at least 5000, preferably at least 10,000 and most preferably at least 15,000.

Polyoxyethylene-polyoxypropylene block copolymer adducts of ethylene diamine which can be used may be represented by the following formula:



(V)

wherein a and b are integers such that the copolymer may have (1) a hydrophobe base molecular weight of at least 2000, preferably at least 3000, and most preferably at least 4500, (2) a hydrophile content of at least 60%, preferably at least 70% by weight, and (3) a total average molecular weight of at least 5000, preferably at least 10,000, and most preferably at least 15,000.

The hydrophobe base of the copolymer of formula V is prepared by adding propylene oxide for reaction at the site of the four reactive hydrogen atoms on the amine groups of ethylene diamine. An ethylene oxide residue is used to cap the hydrophobe base. These hydrophile polyoxyethylene groups are controlled so as to constitute at least 60%, preferably at least 70% by weight, and most preferably at least 80% by weight of the copolymer.

The procedure used to prepare aqueous solutions which form gels of the polyoxyalkylene block copolymers is well known. Either a hot or cold process for forming the solutions can be used. A cold technique involves the steps of dissolving the polyoxyalkylene block copolymer at a temperature of 5° to 10° C in water. When solution is complete the system is brought to room temperature whereupon it forms a gel. If the hot process of forming the gel is used the polymer is added to water heated to a temperature of 75°C to 85°C with slow stirring until a clear homogenous solution is obtained. Upon cooling to room temperature, a clear gel is formed. Block copolymer gels containing polyoxybutylene hydrophobes must be prepared by the above hot process, since these will not liquify at low temperatures.

As used herein, the term "gel" is defined as a solid or semisolid colloid containing a certain quantity of water. The colloidal solution with water is often called a "hydrosol".

The organic compound initiator which is utilized in the process for the preparation of the polyoxyalkylene block copolymers generally is water or an organic compound and can contain a plurality of reactive hydrogen atoms. Preferably, Y In formulae I and II above is defined as derived from a water soluble organic compound having 1 to 6 carbon atoms and containing x reactive hydrogen atoms where x has a value of at least 2. Falling within the scope of the compounds from which Y is derived are water soluble organic compounds such as, for example, propylene glycol, glycerin, pentaerythritol, trimethylolpropane, ethylene diamine, and mixtures thereof and the like.

The oxypropylene chains can optionally contain small amounts of at least one of oxyethylene or oxybutylene groups. Oxyethylene chains can optionally contain small amounts of at least one of oxypropylene or oxybutylene groups. Oxybutylene chains can optionally contain small amounts of at least one of ethylene or oxypropylene groups. The physical form of the polyoxyalkylene block copolymers can be a viscous liquid, a paste, or a solid granular material depending upon the molecular weight of the polymer. Useful polyoxyalkylene block copolymers generally have a total average molecular weight of 5000 to 50,000, preferably 5,000 to 35,000 and most preferably 10,000 to 25,000.

Preferably the polyoxyalkylene block copolymer is applied to surgically injured tissue as an aqueous solution which upon contact with living mammalian tissue forms a firm, adherent gel. Where an polyoxyalkylene block copolymer is a viscous liquid or paste, these compositions can be applied without dilution to areas of surgical injury in the abdominal or thoracic cavities. Where the block copolymers have the physical form of a paste or granular solid, it may be necessary or desirable to incorporate therewith either a low molecular weight liquid block copolymer, as defined herein, and/or a carrier liquid (solvent or a diluent).

The carrier solvent or diluent must be selected so as to be physiologically acceptable. Water, glycerine, and sorbitol are acceptable as solvents for the block copolymers. Other possibly acceptable solvents for the block copolymers are ethanol, isopropanol, n-butyl alcohol, tertiary butyl alcohol, cyclohexanone, hexylene glycol (2 methyl-2,4-pentanediol), butoxyethoxypropanol, butyl cellosolve®, butyl carbitol®, tetrahydrofuran, polyethylene glycols (liquid grades), polypropylene glycols having a molecular weight of less than 800, certain ketones, and propylene glycol. Generally, the block copolymers are insoluble in glycerol and mineral

oil but these materials can be utilized as diluents, alone or in mixtures with the above solvents provided such mixtures are acceptable physiologically for application to injured tissue. Not all the above listed solvents for the block copolymers can be utilized in this invention since some of these may not be physiologically acceptable for application to an injured tissue or otherwise.

The following Examples illustrate the various aspects of the invention. Where not otherwise specified throughout this specification and claims, temperatures are given in degrees centigrade, and parts, percentages, and proportions are by weight.

EXAMPLE 1

An aqueous solution was made of a polyoxyethylene-polyoxypropylene block copolymer having the structure generically shown as formula IV and having a polyoxypropylene hydrophobe base average molecular weight of 4000, a total average molecular weight of 11,500, and containing oxyethylene groups in the amount of 70% by weight of the total weight of copolymer. This copolymer is sold under the trademark PLURONIC® F-127 by the BASF Corporation, Parsippany, New Jersey. A solution was made by dissolving said polymer in cold (4 • C) distilled water to give a concentration of 30% by weight in accordance with the cold process described above for forming aqueous solutions. More specific solution procedures are described in "Artificial Skin I Preparation and Properties of Pluronic F-127 Gels for Treatment of Burns", J. Biomed. Mater. Res. 6, 527, 1972. The block copolymer has the formula:

$$H[OCH_2\ CH_2]_{49}\ [OCH\ CH_2]_{67}\ [OCH_2\ CH_2]_{49}\ OH \qquad (VI)$$

(the CH_3 group is attached to the CH of the middle block)

This solution is a liquid at 4 • C and forms a gel which is adherent to living tissue upon contact. This solution was applied at 4 • C in the following experiments.

EXAMPLES 2-23

The following test procedure was utilized in order to determine the effect of the solution of Example 1 on surgically injured rats. Twenty-two female Sprague-Dawley rats having a 300-400 gram body weight were anesthetized with pentabarbital sodium (30 milligrams per kilogram of body weight) by application intraperitoneally through the left lumbar region of the ventral abdominal wall. The abdomen was thereafter opened by a 5 centimeter midline vertical incision subsequent to cleansing of the abdominal surface with povidone-iodine solution and removing hair by shaving. A one centimeter segment of each uterine horn was stipped of serosa and an opposing one square centimeter of parietal peritoneum was excised, including the underlying muscle layer. Hemostasis was not attained.

Subsequently, the block copolymer solution of Example 1 was applied at a temperature of 4 • C to both the surgically injured area of the uterine horn and the parietal peritoneum surgical injury but only on one side of the abdomen. After the first application had formed a gel, a second layer of block copolymer solution was applied. Approximately 0.5 to 1.5 cubic centimeters of the block copolymer solution was applied depending upon the amount necessary to adequately cover (on one side of the abdomen) both the surgically injured one centimeter segment of the uterine born and the surgically injured one square centimeter area of parietal peritoneal tissue.

The remaining side of the abdomen which was surgically injured in the same manner was left untreated. The portion of the uterine born which was stripped of serosa was then attached within 0.5 centimeter of the surgical injury to the peritoneal parietal area by a single 3-0 VICRYL ligature suture. This was done to ensure that the injured surface of the uterine horn remained in close proximity to the surgical injury of the parietal area of the peritoneum until re-peritonealization had occurred. The abdominal wall was closed with a single layer of interrupted 0-0 VICRYL suture and 21 days later each animal was sacrificed and the abdomen was examined for the presence of adhesions.

The following grading system was used to evaluate the results obtained:

0 = no adhesions observed.
1 = adhesions on 25% of the surgically injured area.
2 = adhesions on 50% of the surgically injured area.
3 = adhesions on 100% of the surgically injured area.

The tenacity of the adhesion which formed was evaluated according to the following grading system.

0.0 = no resistance to separation.

0.5 = moderate force of separation required to rupture the adhesion.

1.0 = strong force or cutting necessary for separation.

A rating for the results obtained was obtained by adding the results in each of the grading systems. Results therefore would range from 0.0 to 4.0 for each surgically injured area evaluated. The data were analyzed by a rank sum test and also by analysis of variance.

Since the bilaterally surgically injured areas of each rat were treated with block copolymer solution only unilaterally, each rat served as its own control. Twenty of the 22 rats used in the evaluation survived a 21 day period prior to sacrifice. Two animals died from failure to adequately close the abdominal incision to seal the peritoneal cavity and its contents.

Nineteen of the 20 surviving animals developed adhesions on the untreated control side of the abdomen. The combined score for the untreated control, including area and tenacity of the adhesions, averaged 3.2. On the block copolymer solution treated side of the abdomen, in 8 of the 20 surviving rats, some degree of adhesion was noted. The combined score, for the block copolymer treated areas including area and tenacity of adhesions in these 8 rats averaged only 1.63. These results taken with the results for the block copolymer treated side of the remaining 12 rats having no adhesions provided a combined average score of only 0.7. This difference is considered statistically significant at the p less than 0.005 level.

EXAMPLES 24-46

The procedure of Examples 2-23 is repeated utilizing a 20% by weight aqueous solution of a polyoxybutylene-based block copolymer having the structure generically shown as formula III and having a polyoxybutylene hydrophobe base having an average molecular weight of 3000 and a total average molecular weight of 10,000. Substantially similar results are obtained following the test procedure of Examples 2-23.

EXAMPLES 47-69

Utilizing a 30% by weight aqueous solution of a polyoxyethylene-polyoxypropylene block copolymer having the structure generically shown in formula I and having a polyoxypropylene hydrophobe base molecular weight of 2000, a polyoxyethylene content of 70% by weight, and a total average molecular weight of 5000, the test procedure of Examples 2-23 is repeated to obtain substantially the same results.

EXAMPLES 70-92

The procedure of Examples 2-23 is repeated using a 30% by weight aqueous solution of a polyoxyethylene-polyoxypropylene block copolymer adduct of ethylene diamine having a hydrophobe molecular weight of 1500 and a total average molecular weight of 2500, said copolymer having a hydrophile content of 60% by weight and a total average molecular weight of 5500. Substantially similar results are obtained.

Claims

1. A composition for use in the treatment of the mammalian body by reducing post-surgical adhesion formation/reformation following surgical injury to mammalian peritoneal or pleural cavity tissue or organs situated therein which comprises a component which is liquid at 4°C and which is a gel at mammalian body temperature, said component comprises a polyoxyalkylene block copolymer of formula:

$$Y[(A)_n - E - H]_x \quad (I)$$

wherein A is an oxyalkylene moiety having an oxygen/carbon atom ratio of less than 0.5, x is at least 1, Y is derived from water or an organic compound containing x reactive hydrogen atoms, E is a polyoxyethylene moiety, n has a value such that the average molecular weight of A is at least 500, as determined by the hydroxyl number of an intermediate of formula:

$$Y[(A)_n - H]_x \quad (II)$$

and the total average molecular weight of the polyoxyalkylene block copolymer is at least 5000.

2. A composition according to claim 1, wherein A is a polyoxyalkylene moiety, x is at least 2, and E is polyoxyethylene moiety constituting at least 60% by weight of the copolymer.

3. A composition according to claim 2, wherein E is a polyoxyethylene moiety constituting at least 70% by weight of the copolymer.

4. A composition according to any of claims 1 to 3, wherein Y is derived from a water-soluble compound having 1 to 6 carbon atoms.

5. A composition according to claim 4, wherein Y is derived from a compound selected from propylene glycol, glycerin, pentaerythritol, trimethylolpropane, ethylenediamine, and mixtures thereof.

6. A composition according to any of claims 1 to 5, wherein the copolymer is selected from a polyoxyethylene-polyoxybutylene block copolymer, a polyoxyethylene-polyoxypropylene block copolymer and mixtures thereof, and wherein the composition includes physiologically acceptable carrier liquid.

7. A composition according to claim 6, wherein the copolymer is selected from block copolymers which form aqueous gels at a concentration of 10 to 40% by weight of the total weight of said composition.

8. A composition according to claim 7, wherein the carrier liquid is water.

9. A composition according to any of claims 6 to 8, wherein Y is derived from propylene glycol, A is the residue of propylene oxide, and the intermediate of Formula II has an average molecular weight of at least 900.

10. A composition according to any of claims 6 to 8, wherein Y is derived from butylene glycol, A is the residue of butylene oxide, and the intermediate of Formula II has an average molecular weight of at least 500.

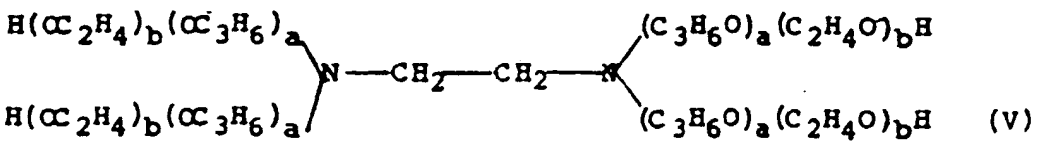
11. A composition according to any of claims 6 to 10, wherein the copolymer has the formula :

$$HO(C_2H_4O)_b(C_4H_8O)_a(C_2H_4O)_bH \quad (III)$$

wherein a is an integer such that the hydrophobe base represented by (C_4H_8O) has a molecular weight of at least 1000, as determined by hydroxyl number, or

$$HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH \quad (IV)$$

wherein a is an integer such that the hydrophobe base represented by (C_3H_6O) has a molecular weight of at least 1500 average molecular weight, as determined by hydroxyl number, or



(V)

wherein a and b are integers such that the copolymer has a hydrophobe molecular weight of at least 2000.

12. A composition according to claims 1-5, wherein the polyoxyalkylene moiety is derived from an alkylene oxide selected from butylene oxide, propylene oxide, and mixtures thereof.

13. A composition according to claim 12, wherein the composition includes a physiologically acceptable non-aqueous carrier in an amount sufficient to solubilize or disperse the copolymer.

14. A composition according to claim 13, wherein the copolymer is selected from block copolymers which have a total average molecular weight of at least 10,000 and which form aqueous gels at a concentration of 10 to 40% by weight.

15. A composition according to claim 14, wherein the copolymer is a polyoxyethylene-polyoxypropylene block copolymer wherein the average molecular weight of A is at least 1200, and the total molecular weight of the copolymer is at least 10,000.

16. A composition according to claim 15, wherein intermediate of Formula II is prepared by initiation with propylene glycol, has a molecular weight of at least 1500, and the composition contains a humectant selected from at least one of propylene glycol, glycerine, and sorbitol.

17. A composition according to claim 16, wherein the intermediate of Formula II is prepared by initiation with propylene glycol and has a molecular weight of at least 1500, and the humectant is propylene glycol.

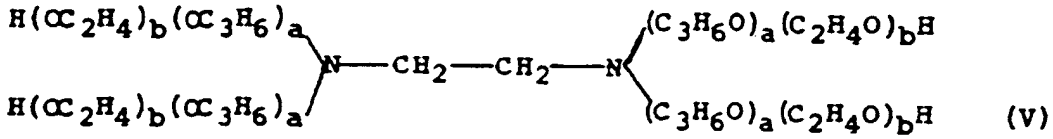
18. A composition according to any of claims 1 to 5, 12 or 13, wherein the copolymer has the formula:

$$HO(C_2H_4O)_b(C_4H_8O)_a(C_2H_4O)_bH \quad (III)$$

wherein a is an integer such that the hydrophobe base represented by (C_4H_8O) has a molecular weight of at least 500 as determined by hydroxyl number, or

$$HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH \quad (IV)$$

wherein a is an ingeger such that the hydrophobe base represented by (C_3H_6O) has a molecular weight of at least 900 average molecular weight, as determined by hydroxyl number, or



(V)

wherein a and b are integers such that the copolymer has a hydrophobe molecular weight of at least 800.

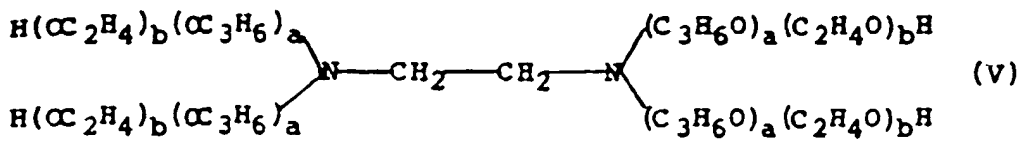
19. A composition according to claim 18 wherein the copolymer has the formula:

$$HO(C_2H_4O)_b(C_4H_8O)_a(C_2H_4O)_bH \quad (III)$$

wherein a is an integer such that the hydrophobe base represented by (C_4H_8O) has a molecular weight of at least 500 as determined by hydroxyl number and the copolymer has a total average molecular weight of at least 15,000, or

$$HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH \quad (IV)$$

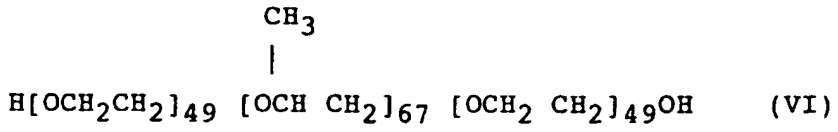
wherein a is an integer such that the hydrophobe base represented by (C_3H_6O) has a molecular weight of at least 900 average molecular weight, as determined by hydroxyl number and the copolymer has a total average molecular weight of at least 15,000 or



(V)

wherein a and b are integers such that the copolymer has a hydrophobe molecular weight of at least 1500 and a total average molecular weight of at least 15,000.

20. A composition according to any of claims 1 to 19, wherein the polyoxyalkylene block copolymer has the formula



(VI)

and is present in the amount of 10 to 40% by weight of the total weight of the composition.

21. A composition according to claim 20, wherein the polyoxyalkylene block copolymer is present in the amount of 15 to 30% by weight in the composition.

22. The use of a composition as defined in any of claims 1 to 21 for the manufacture of a medicament for reducing post-surgical adhesion formation/reformation following surgical injury to mammalian peritoneal or pleural cavity tissue or organs-situated therein.

Patentansprüche

1. Zusammensetzung zur Verwendung bei der Behandlung des Säugetierkörpers durch Verminderung von postoperativer Bildung/Rückbildung von Adhäsion im Anschluß an chirurgische Wunden von Geweben von peritonealen oder pleuralen Hohlräumen oder von hierin befindlichen Organen von Säugetieren, welches eine Komponente umfaßt, die bei 4° C flüssig ist und ein Gel bei Säugetier-Körpertemperatur ist, wobei diese Komponente ein Polyoxyalkylen-Blockcopolymeres der Formel:

$$Y[(A)_n - E - H]_x \quad (I)$$

umfaßt, worin A eine Oxyalkyleneinheit mit einem Sauerstoff/Kohlenstoff-Verhältnis von weniger als 0,5 ist, x wenigstens 1 beträgt, Y von Wasser oder einer x reaktionsfähige Wasserstoffatome besitzenden, organischen Verbindung abstammt, E eine Polyoxyethyleneinheit ist, n einen solchen Wert hat, daß das Durchschnittsmolekulargewicht von A wenigstens 500 ist, bestimmt durch die Hydroxylzahl eines Zwischenproduktes der Formel:

$$Y[(A)_n - H]_x \quad (II)$$

und das Gesamtdurchschnittsmolekulargewicht des Polyoxyalkylen-Blockcopolymeren wenigstens 5.000 beträgt.

2. Zusammensetzung nach Anspruch 1, worin A eine Polyoxyalkyleneinheit ist, x wenigstens 2 beträgt und E Polyoxyethyleneinheit ist, die wenigstens 60 Gew.-% des Copolymeren ausmacht.

3. Zusammensetzung nach Anspruch 2, worin E eine Polyoxyethyleneinheit ist, die wenigstens 70 Gew.-% des Copolymeren ausmacht.

4. Zusammensetzung nach einem der Ansprüche 1 bis 3, worin Y von einer wasserlöslichen Verbindung mit 1 bis 6 Kohlenstoffatomen abstammt.

5. Zusammensetzung nach Anspruch 4, worin Y von einer aus Propylenglykol, Glycerin, Pentaerythrit, Trimethylolpropan, Ethylendiamin und Mischungen hiervon ausgewählten Verbindung abstammt.

6. Zusammensetzung nach einem der Ansprüche 1 bis 5, worin das Copolymere aus einem Polyoxyethylen-Polyoxybutylen-Blockcopolymeren, einem Polyoxyethylen-Polyoxypropylen-Blockcopolymeren und Mischungen hiervon ausgewählt ist, und worin die Zusammensetzung physiologisch annehmbare Trägerflüssigkeit einschließt.

7. Zusammensetzung nach Anspruch 6, worin das Copolymere aus Blockcopolymeren ausgewählt ist, die wässrige Gele bei einer Konzentration von 10 bis 40 Gew.-% des Gesamtgewichtes dieser Zusammensetzung bilden.

8. Zusammensetzung nach Anspruch 7, worin die Trägerflüssigkeit Wasser ist.

9. Zusammensetzung nach einem der Ansprüche 6 bis 8, worin Y von Propylenglykol abstammt, A der Rest von Propylenoxid ist und das Zwischenprodukt der Formel II ein Durchschnittsmolekulargewicht von wenigstens 900 hat.

10. Zusammensetzung nach einem der Ansprüche 6 bis 8, worin Y von Butylenglykol abstammt, A der Rest von Butylenoxid ist und das Zwischenprodukt der Formel II ein Durchschnittsmolekulargewicht von wenigstens 500 hat.

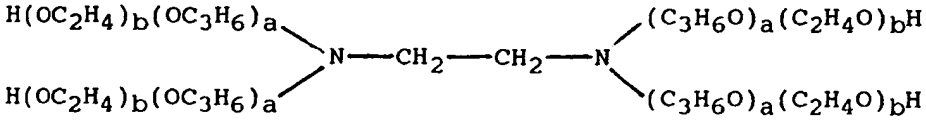
11. Zusammensetzung nach einem der Ansprüche 6 bis 10, worin das Copolymere die Formel hat:

$$HO(C_2H_4O)_b(C_4H_8O)_a(C_2H_4O)_bH \quad (III)$$

worin a eine solche ganze Zahl ist, daß die durch (C_4H_8O) wiedergegebene, hydrophobe Basis ein Molekulargewicht von wenigstens 1.000, bestimmt durch die Hydroxylzahl, hat, oder

$$HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH \quad (IV)$$

worin a eine solche ganze Zahl ist, daß die durch (C_3H_6O) wiedergegebene, hydrophobe Basis ein Molekulargewicht von wenigstens 1.500 Durchschnittsmolekulargewicht, bestimmt durch die Hydroxylzahl, hat, oder



(V)

worin a und b solche ganze Zahlen sind, daß das Copolymere ein hydrophobes Molekulargewicht von wenigstens 2.000 hat.

12. Zusammensetzung nach den Ansprüche 1 - 5, worin die Polyoxylalkyleneinheit von einem aus Butylenoxid, Propylenoxid und Mischungen hiervon ausgewählten Alkylenoxid abstammt.

13. Zusammensetzung nach Anspruch 12, worin die Zusammensetzung einen physiologisch annehmbaren, nicht-wässrigen Träger in einer ausreichenden Menge zur Solubilisierung oder zum Dispergieren des Copolymeren einschließt.

14. Zusammensetzung nach Anspruch 13, worin das Copolymere aus Blockcopolymeren ausgewählt ist, die ein Gesamtdurchschnittsmolekulargewicht von wenigstens 10.000 besitzen und die wässrige Gele bei einer Konzentration von 10 bis 40 Gew.-% bilden.

15. Zusammensetzung nach Anspruch 14, worin das Copolymere ein Polyoxyethylen-Polyoxypropylen-Blockcopolymeres ist, in dem das Durchschnittsmolekulargewicht von A wenigstens 1.200 beträgt, und das Gesamtmolekulargewicht des Copolymeren wenigstens 10.000 beträgt.

16. Zusammensetzung nach Anspruch 15, worin das Zwischenprodukt der Formel II durch Initiieren mit Propylenglykol hergestellt ist, ein Molekulargewicht von wenigstens 1.500 hat, und die Zusammensetzung ein aus wenigstens einer der Verbindungen Propylenglykol, Glycerin und Sorbit ausgewähltes, feuchthaltendes Mittel enthält.

17. Zusammensetzung nach Anspruch 16, worin das Zwischenprodukt der Formel II durch Initiieren mit Propylenglykol hergestellt ist und ein Molekulargewicht von wenigstens 1.500 hat, und das feuchthaltende Mittel Propylenglykol ist.

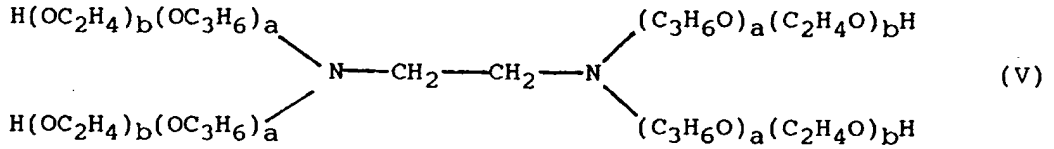
18. Zusammensetzung nach einem der Ansprüche 1 bis 5, 12 oder 13, worin das Copolymere die Formel hat:

$HO(C_2H_4O)_b(C_4H_8O)_a(C_2H_4O)_bH$ (III)

worin a eine solche ganze Zahl ist, daß die durch (C_4H_8O) wiedergegebene hydrophobe Basis ein Molekulargewicht von wenigstens 500, bestimmt durch die Hydroxylzahl, hat, oder

$HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH$ (IV)

worin a eine solche ganze Zahl ist, daß die durch (C_3H_6O) wiedergegebene hydrophobe Basis ein Molekulargewicht von wenigstens 900 Durchschnittsmolekulargewicht, bestimmt durch die Hydroxylzahl, hat, oder



(V)

worin a und b solche ganze Zahlen sind, daß das Copolymere ein hydrophobes Molekulargewicht von wenigstens 800 hat.

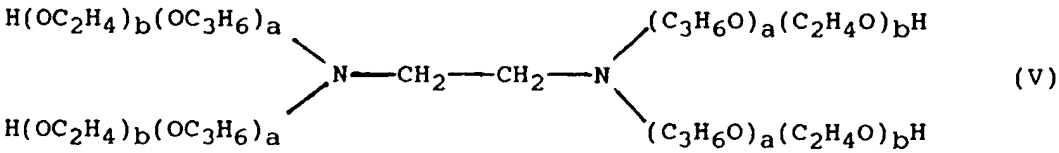
19. Zusammensetzung nach Anspruch 18, worin das Copolymere die Formel hat:

$HO(C_2H_4O)_b(C_4H_8O)_a(C_2H_4O)_bH$ (III)

worin a eine solche ganze Zahl ist, daß die durch (C_4H_8O) wiedergegebene, hydrophobe Basis ein Molekulargewicht von wenigstens 500, bestimmt durch die Hydroxylzahl, hat, und das Copolymere ein Gesamtdurchschnittsmolekulargewicht von wenigstens 15.000 besitzt, oder

$HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH$ (IV)

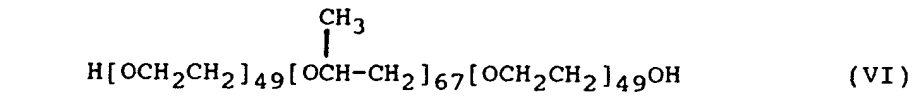
worin a eine solche ganze Zahl ist, daß die durch (C_3H_6O) wiedergegebene, hydrophobe Basis ein Molekulargewicht von wenigstens 900 Durchschnittsmolekulargewicht, bestimmt durch die Hydroxylzahl, hat, und das Copolymere ein Gesamtdurchschnittsmolekulargewicht von wenigstens 15.000 besitzt, oder



(V)

worin a und b solche ganze Zahlen sind, daß das Copolymere ein hydrophobes Molekulargewicht von wenigstens 1.500 und ein Gesamtdurchschnittsmolekulargewicht von wenigstens 15.000 hat.

20. Zusammensetzung nach einem der Ansprüche 1 bis 19, worin das Polyoxyalkylen-Blockcopolymere die Formel hat:



$$H[OCH_2CH_2]_{49}[OCH(CH_3)-CH_2]_{67}[OCH_2CH_2]_{49}OH \qquad (VI)$$

und in einer Menge von 10 bis 40 Gew.-% des Gesamtgewichtes der Zusammensetzung vorhanden ist.

21. Zusammensetzung nach Anspruch 20, worin das Polyoxyalkylen-Blockcopolymere in der Menge von 15 bis 30 Gew.-% in der Zusammensetzung vorhanden ist.

22. Verwendung einer Zusammensetzung entsprechend der Definition in einem der Ansprüche 1 bis 21 zur Herstellung eines Medikamentes zur Verminderung von postoperativer Bildung/Rückbildung von Adhäsion im Anschluß an chirurgische Wunden von Geweben von peritonealen oder pleuralen Hohlräumen oder von hierin befindlichen Organen von Säugetieren.

Revendications

1. Composition destinée à être utilisée dans le traitement du corps de mammifères en réduisant la formation/reformation d'adhérences post-chirurgicales à la suite d'une lésion chirurgicale au tissu de la cavité péritonéale ou pleurale du mammifère, ou des organes situés dans cette cavité, comprenant un composant qui est liquide à 4°C et qui forme un gel à la température du corps du mammifère, ce composant comprenant un copolymère en bloc de polyoxyalkylène de formule :

$$Y[(A)_n - E - H]_x \qquad (I)$$

caractérisée en ce que A est une part d'oxyalkylène présentant un rapport atomique d'oxygène/carbone de moins de 0,5, x est au moins égal à 1, Y est dérivé d'eau ou d'un composé organique contenant x atomes d'hydrogène réactifs, E est une part de polyoxyéthylène, n présente une valeur telle que le poids moléculaire moyen de A soit d'au moins 500, comme déterminé par le nombre hydroxyle d'un intermédiaire de formule :

$$Y[(A)_n - H]_x \qquad (II)$$

et le poids moléculaire moyen total du copolymère en bloc de polyoxyalkylène est d'au moins 5000.

2. Composition selon la revendication 1, caractérisée en ce que A est une part de polyoxyalkylène, x est égal à au moins 2 et E est une part de polyoxyéthylène constituant au moins 60 % en poids du copolymère.

3. Composition selon la revendication 2, caractérisée en ce que E est une part de polyoxyéthylène constituant au moins 70 % en poids du copolymère.

4. Composition selon l'une quelconque des revendications 1 à 3, caractérisée en ce que Y est dérivé d'un composé soluble dans l'eau comportant de 1 à 6 atomes de carbone.

5. Composition selon la revendication 4, caractérisée en ce que Y est dérivé d'un composé choisi parmi le propylène glycol, la glycérine, le pentaérythritol, le triméthylolpropane, l'éthylène diamine, et des mélanges de ces produits.

6. Composition selon l'une quelconque des revendications 1 à 5, caractérisée en ce que le copolymère est choisi parmi un copolymère en bloc de polyoxyéthylène-polyoxybutylène, un copolymère en bloc de polyoxyéthylène-polyoxypropylène, et des mélanges de ces copolymères, et dans laquelle la

composition comprend un liquide porteur physiologiquement acceptable.

7. Composition selon la revendication 6, caractérisée en ce que le copolymère est choisi parmi des copolymères en bloc qui forment des gels aqueux à une concentration de 10 % à 40 % du poids total de la composition.

8. Composition selon la revendication 7, caractérisée en ce que le liquide porteur est de l'eau.

9. Composition selon l'une quelconque des revendications 6 à 8, caractérisée en ce que Y est dérivé de glycol de propylène, A est le résidu d'oxyde de propylène, et l'intermédiaire de la Formule II présente un poids moléculaire moyen d'au moins 900.

10. Composition selon l'une quelconque des revendications 6 à 8, caractérisée en ce que Y est dérivé de glycol de butylène, A est le résidu d'oxyde de butylène, et l'intermédiaire de la Formule II présente un poids moléculaire moyen d'au moins 500.

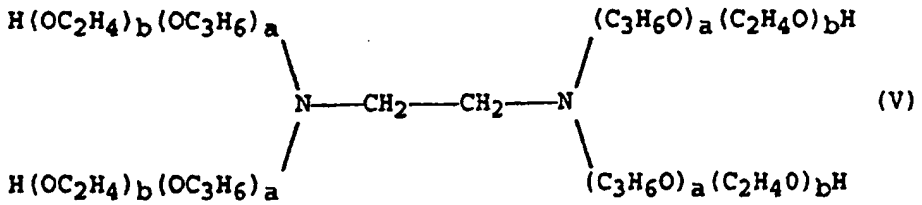
11. Composition selon l'une quelconque des revendications 6 à 10, caractérisée en ce que le copolymère présente la formule :

$HO(C_2H_4O)_b(C_4H_8O)_a(C_2H_4O)_bH$ (III)

en ce que a est un nombre entier de façon que la base hydrophobe représentée par (C_4H_8O) présente un poids moléculaire d'au moins 1000, comme déterminé par le nombre hydroxyle, ou

$HO(C_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH$ (IV)

en ce que a est un nombre entier de façon que la base hydrophobe représentée par (C_3H_6O) présente un poids moléculaire moyen d'au moins 1500, comme déterminé par le nombre hydroxyle, ou



(V)

en ce que a et b sont des nombres entiers de façon que le copolymère présente un poids moléculaire d'hydrophobe d'au moins 2000.

12. Composition selon l'une des revendications 1 à 5, caractérisée en ce que la part de polyoxyalkylène est dérivée d'un oxyde d'alkylène choisi parmi l'oxyde de butylène, l'oxyde de propylène, et des mélanges de ces oxydes.

13. Composition selon la revendication 12, caractérisée en ce que la composition comprend un porteur non-aqueux acceptable physiologiquement, dans une proportion suffisante pour dissoudre ou disperser le copolymère.

14. Composition selon la revendication 13, caractérisée en ce que le copolymère est choisi parmi les copolymères en bloc qui présentent un poids moléculaire moyen total d'au moins 10 000 et qui forment des gels aqueux à une concentration de 10 % à 40 % en poids.

15. Composition selon la revendication 14, caractérisée en ce que le copolymère est un copolymère en bloc de polyoxyéthylène-polyoxypropylène dans lequel le poids moléculaire moyen de A est d'au moins 1200 et le poids moléculaire total du copolymère est d'au moins 10 000.

16. Composition selon la revendication 15, caractérisée en ce que l'intermédiaire de la Formule II est préparé par initiation par du propylène glycol et présente un poids moléculaire d'au moins 1500, tandis que la composition contient un humectant choisi parmi l'un au moins du propylène glycol, de la glycérine et du sorbitol.

17. Composition selon la revendication 16, caractérisée en ce que l'intermédiaire de la Formule II est préparé par initiation par du glycol de propylène et présente un poids moléculaire d'au moins 1500, tandis que l'humectant est du propylène glycol.

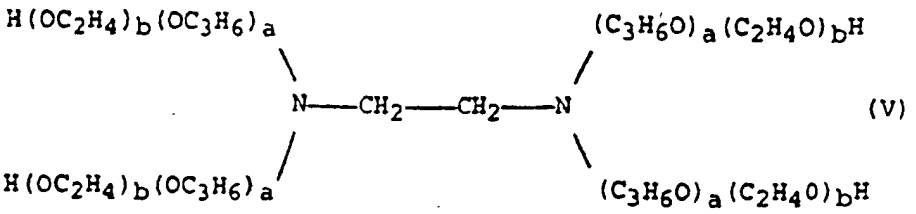
18. Composition selon l'une quelconque des revendications 1 à 5, 12 ou 13, caractérisée en ce que le copolymère présente la formule :

$HO(C_2H_4O)_b(C_4H_8O)_a(C_2H_4O)_bH$ (III)

en ce que a est un nombre entier de façon que la base hydrophobe représentée par (C_4H_8O) présente un poids moléculaire d'au moins 500, comme déterminé par le nombre hydroxyle, ou

$H(OC_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH$ (IV)

en ce que a est un nombre entier de façon que la base hydrophobe représentée par (C_3H_6O) présente un poids moléculaire moyen d'au moins 900, comme déterminé par le nombre hydroxyle, ou



(V)

en ce que a et b sons des nombres entiers de façon que le copolymère présente un poids moléculaire d'hydrophobe d'au moins 800.

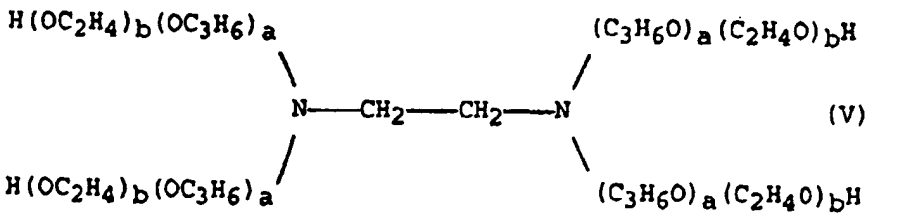
19. Composition selon la revendication 18, caractérisée en ce que le copolymère présente la formule :

$HO(C_2H_4O)_b(C_4H_8O)_a(C_2H_4O)_bH$ (III)

en ce que a est un nombre entier de façon que la base hydrophobe représentée par (C_4O_8O) présente un poids moléculaire d'au moins 500, comme déterminé par le nombre hydroxyle, et le copolymère présente un poids moléculaire moyen total d'au moins 15 000, ou

$H(OC_2H_4O)_b(C_3H_6O)_a(C_2H_4O)_bH$ (IV)

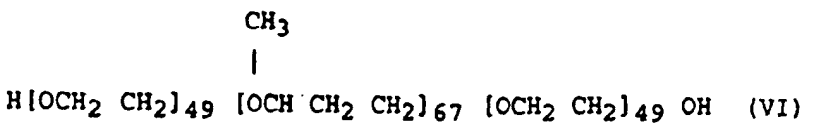
en ce que a est un nombre entier de façon que la base hydrophobe représentée par (C_3H_6O) présente un poids moléculaire moyen d'au moins 900, comme déterminé par le nombre hydroxyle, et le copolymère présente un poids moléculaire moyen total d'au moins 15 000, ou



(V)

en ce que a et b sont des nombres entiers de façon que le copolymère présente un poids moléculaire hydrophobe d'au moins 1500 et un poids moléculaire moyen total d'au moins 15 000.

20. Composition selon l'une quelconque des revendications 1 à 19, caractérisée en ce que le copolymère en bloc de pôlyoxyalkylène présente la formule



et est présent dans la proportion de 10 % à 40 % du poids total de la composition.

21. Composition selon la revendication 20, caractérisée en ce que le copolymère en bloc de polyoxyalkylène est présent dans la proportion de 15 % à 30 % du poids de la composition.

22. Utilisation d'une composition telle que définie dans l'une quelconque des revendications 1 à 21, pour la fabrication d'un médicament destiné à réduire la formation/reformation d'adhérences post-chirurgicales à la suite d'une lésion chirurgicale au tissu de la cavité péritonéale ou pleurale d'un mammifère, ou aux organes situés dans cette cavité.